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Psychosocial/Survivorship Issues in Breast Cancer: Are we doing better?

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Abstract

Modern breast cancer treatment offers many women greater prospects of cure or lengthier, good quality survival than was possible in the past. Advances include:- improved diagnostic and staging procedures, sophisticated onco-plastic surgery, enhanced radiotherapy techniques and targeted systemic therapies. Much more attention has also been paid to cancer care delivery and access to specialist nurses, counsellors, support groups and services provided by breast cancer charities. However there are some concerns that these considerable improvements in treatment delivery and clinical outcomes have not led to similar benefits in the psychosocial, functional and sexual well-being of women. The impact that non-life threatening, long-term iatrogenic harms of otherwise efficacious anti-cancer treatments has on patients is often over-looked; this is in part due to the emphasis given to physician reported safety data in trials and the general exclusion of patient reported outcomes(PROs). A failure to utilise reliable PRO measures has meant that some problems are under-reported which consequently has hampered much needed research into ameliorative interventions. Systematic monitoring of quality of life-threatening side-effects would permit early implementation of effective interventions and enhance long-term survivorship. Some examples of the pervasive difficulties that continue to affect survivors and evidence that certain interventions might help, are provided in this commentary.

Introduction

The past 3 decades have seen some extraordinary advances made in breast cancer treatment that offer women greater prospects of cure or lengthier, good quality

survival. Wide publicity is given quite rightly to better diagnostics, improved and less radical surgical techniques, increasing recognition of the need to manage the axilla, specialist oncoplastic surgeons producing more acceptable cosmetic outcomes, less damaging radiotherapy techniques and new procedures such as intraoperative radiotherapy that reduce treatment time and hospital visits. The explosion in knowledge regarding the genomics and molecular biology of breast cancer has also increased the number of chemotherapeutic options; trials report regularly the Progression Free Survival (PFS) and Overall Survival (OS) benefits of the newer systemic cytotoxic, hormone, and targeted therapies.

Unfortunately, nothing comes without cost and despite these laudable therapeutic breakthroughs, considerable psychosocial and iatrogenic harms continue to be created by the diagnosis of breast cancer and its treatment. Most of the treatment related side-effects are acute, but some can be long-term impacting quality of life, and many women remain plagued by a plethora of physical, functional, emotional, financial and social challenges. Although responses vary at different stages of the disease trajectory, the impact of these issues preoccupies some women constantly. Importantly as few patients inhabit complete social vacuums, many of their concerns related to diagnosis and treatment, also affect others family members and friends. One positive outcome of psychosocial research exploring these areas of concern and the advocacy demands by women themselves, has been the increased awareness of the need to provide access to specialist nurses, patient navigators, counsellors and support groups. In tandem, some influential bodies, such as the Institute of Medicine (IOM), also made recommendations to promote evidence-based, comprehensive, compassionate and coordinated survivorship care plans for all people diagnosed with cancer (1).

Despite all the new treatment options with their resultant improved clinical outcomes, it is questionable whether or not these endeavours have led to many comparable, measurable benefits in patients' psychosocial, functional, occupational and sexual well-being. In this commentary we will outline some of the primary concerns that women with breast cancer continue to experience from diagnosis through survivorship, and then review some of the evidenced-based interventions that have made a difference.

Psychological morbidity

Much psychosocial research over the past 30 years has focused on the prevalence of psychological morbidity and has produced mixed results; some reports suggest that the prevalence of mood disorders such as anxiety and depression is high at diagnosis and is unremitting (2) whilst others have found a decline over time and little difference from that seen in age-matched controls without breast cancer. An interesting recent meta-analysis of 43 studies compared the prevalence of mood disorders in cancer survivors with their spouses (17 studies) and with healthy controls (26 studies). In a pooled analysis the prevalence of depression of 51,381 cancer survivors was 11.6% compared with 10.2% in 217,630 healthy controls. The prevalence of anxiety was higher - 17.9% in 46,964 cancer survivors compared to 13.9% in 226,467 healthy controls. Of note neither the prevalence of depression nor anxiety differed significantly between survivors and their spouses demonstrating the likely wider family support needs (3).

Unfortunately much of the early research in this area has been hampered by inappropriate measures and methodology (4) and some extremely loose use of nomenclature; general distress is often confused with clinical anxiety states and

depressive or adjustment disorders. This might be due in part to the fact that most criteria for diagnosing anxiety and adjustment disorders were developed for psychiatrically ill not physically ill individuals. Many women with breast cancer do genuinely confront continual and real threats that their cancer will recur; consequently their 'anxiety' could be viewed as neither irrational nor inappropriate. One study of 3,300 long-term survivors (2 years post diagnosis) showed that 47% had a fear of recurrence (5).

Being clear about the precise clinical characteristics of any psychological morbidity is important when determining the most appropriate prevention or screening strategies for those most at risk and ameliorative interventions. The American Society of Clinical Oncology (ASCO) has recently published assessment guidelines (6). A large number of management options is available. Women with clinical depression or anxiety need to be assessed properly and offered appropriate anti-depressant and anxiolytic therapy. For other forms of more generalized distress, a variety of interventions are available that range from cognitive behavior therapy, aromatherapy and massage, visualization, expressive therapeutic writing, art and music therapy. Some publications of well-conducted randomized controlled trials (RCTs) have shown that interventions incorporating elements of mindfulness-based stress reduction can improve mood state and reduce endocrine related side-effects (7) and that yoga can improve quality of life, fatigue, and measures of stress cortisol levels (8).

Iatrogenic harms and side-effects of anti-cancer treatments

Determining healthy long-term adjustment involves more than assessment of psychological morbidity; the deleterious impact exerted by many non-life threatening,

but quality of life threatening iatrogenic harms of otherwise efficacious anti-cancer treatments is often over-looked. Five commonly reported problems--lymphedema, fatigue, vasomotor complaints, sexual dysfunction and cognitive impairment--are considered below.

Lymphedema

Although there have been substantial improvements made within breast cancer surgery, with oncoplastic specialists able to offer procedures that are less radical and improve cosmesis, management of the axilla remains problematic. Some women feel that the aftermath of axillary surgery is worse than the surgery to the breast, creating substantial arm morbidity with lymphedema, pain, loss of sensation and mobility.

Lymphedema in particular remains a problem for many women who have to undergo axillary treatment. A systematic review of 72 studies showed that the overall risk of lymphedema is 17% (9). Those factors influencing risk included more extensive surgery, the number of lymph nodes removed and obesity. There are at least 18 RCTs comparing axillary lymph node dissection with sentinel node biopsy that show the risk of lymphedema to be 19.9% and 5.6% respectively. Sentinel node biopsy has been shown to reduce the amount of axillary surgery required without necessarily compromising survival. It also improves quality of life and reduces arm morbidity generally (10). As systemic therapy has improved outcomes for patients substantially, some doubt whether or not all women with early breast cancer and minimal nodal involvement really need to have axillary surgery at all, so large trials are required to demonstrate the safety of this approach. We do know that efforts to reduce arm morbidity and, importantly, to prevent lymphedema through optimal surgery is absolutely vital as few interventions help after its occurrence. The trials

comparing compression therapy with complex decongestive therapy (massage, exercise and skin care) are sadly equivocal (11).

Fatigue

Fatigue has probably replaced nausea and vomiting as the biggest post-treatment problem; it is usually acute but around 30% of women experience enervating fatigue that may continue for many years. The etiology of fatigue is complex; there is certainly a psychological component as it contributes to and/or is associated with reduced motivation, depression, concentration, impaired activities of daily living and poor overall health related quality of life (12). However pro-inflammatory cytokines have been cited as the most likely underlying biological mechanism (13).

Interventions are very important to initiate early. Although seemingly counter-intuitive, rest is clearly the wrong option and exercise has been shown in many studies to improve not only fatigue but mood state also. An updated Cochrane review of 56 studies, 28 of which were in breast cancer, showed the benefits particularly of aerobic exercise, but not of resistance training (14). Some patients find it quite difficult to engage with exercise programs post-treatment especially if they have not done this regularly prior to breast cancer; so they need considerable encouragement from care-givers, family, and friends or help from a motivational counsellor (15). The more reluctant might be helped by yoga, acupuncture and other mindfulness-based programs although the evidence base for these approaches is less compelling. ASCO have recently published guidelines for the screening, assessment and management of fatigue in adult survivors of cancer generally (16), which could be of benefit to women with breast cancer if implemented as part of their comprehensive cancer care.

Hormone therapy

There are now many data demonstrating the benefits in ER+ women of extending adjuvant therapy to 5 or even 10 years (17). However, it is unfortunate that many of the women being treated with these drugs will derive no benefit whatever and only experience the iatrogenic harms. Side effects such as vasomotor complaints, vaginal dryness, loss of libido, and arthralgia are more than just a minor inconvenience and can lead to treatment discontinuation and suboptimal adherence (18). Patient self-reports compared with physician reports show that many endocrine related side-effects go under-recognized, under-reported, and under-treated (19, 20).

Vasomotor complaints

Vasomotor complaints include hot flushes, cold sweats and night sweats that lead to sleep difficulties which themselves may contribute to fatigue and poor concentration. Estimates vary according to the method of assessment employed and if problems are physician or patient reported, but approximately a third of women experience severe vasomotor side-effects attributable to selective estrogen receptor modulators or aromatase inhibitors (AIs) (21). Although not life-threatening, these unpleasant consequences of treatment have a profound deleterious impact on overall sense of well-being and can affect adherence to oral therapies. Women do need effective non-hormonal treatments to ameliorate vaso-motor side-effects. A Cochrane review (22) looked at interventions that might help. The authors identified 10 pharmacological RCTs that included clonidine, gabapentin, serotonin plus or minus norepinephrine reuptake inhibitors such as venlafaxine, paroxetine, sertraline and fluoxetine. All showed some activity in reducing frequency and severity of hot flushes but there are some contraindications limiting their use in all women. Six non-

pharmacological studies were reviewed; these included some reasonable interventions such as relaxation therapy and acupuncture, together with other more dubious ones such as homeopathy and magnetic devices. Unfortunately, all 6 studies had many methodological limitations; only relaxation therapy reduced both the frequency and the severity of hot flushes. More recent research has shown the benefits of behavioral approaches such as cognitive behavior therapy (CBT). A carefully conducted RCT of usual care or usual care plus group CBT (90 minute weekly sessions for 6 weeks) in women with problematic hot flushes and night sweats showed statistically significant reductions in problems 9 weeks after randomization, which were maintained at 26 weeks (23). The authors point out that as this safe type of behavioral intervention also has the additional benefits of improving mood state, sleep and overall quality of life, it seems useful to incorporate into breast cancer survivorship programs and could be implemented by appropriately trained nurses.

Sexual problems

There are many reports of the sexual difficulties created by breast cancer and its treatment. Vaginal dryness, discharge and dyspareunia combined with a loss of libido exert a negative impact upon patients and their partners. A study of >1000 Australian women showed that 70% of breast cancer survivors experience sexual problems in the 2 years following diagnosis (24). Interestingly >80% of these patients claimed to have had a satisfying sex life prior to diagnosis. Those taking AIs were 50% more likely to report problems than those taking tamoxifen or not having any endocrine therapy. 77% of the sample had hot flushes and night sweats, which were linked to reporting of sexual difficulties. Interventions to help loss of libido, vaginal dryness and dyspareunia are likely to be multi-factorial. Studies suggest that

moisturizers are probably better than lubricants for vaginal dryness, and combinations of moisturizers with pelvic floor exercises and relaxation training have been shown to be useful. (25).

A more general point worth raising regarding the side-effects of otherwise effective treatments for breast cancer, concerns the reliance on clinician reported safety data rather than information collected via patient reported outcome measures in clinical trials. This has led to poor recognition of many of the difficulties some women experience, which in turn has hampered research into much needed ameliorative interventions.

Cognitive Problems

Many women treated with chemotherapy experience memory and attention difficulties, often described as “chemo-brain” or “chemo-fog”. Wide variance exists in the proportions of women reporting problems, partly explained by differences in the neuropsychological tests employed in studies, and the sundry reference data and performance cut offs used when classifying test results (26). Although chemotherapy may be a key contributor to reported dysfunction, it is not the sole cause of “chemo brain” as a third of women perform poorly on cognitive tasks following surgery but prior to starting adjuvant therapies (27). In addition, some studies suggest endocrine therapies play a role (28), although a double blind RCT of anastrozole vs placebo (IBIS II) in postmenopausal women with a high risk of breast cancer found no differences between the groups for either self-reported problems or for any objective cognitive assessment (29). A recent prospective study of 189 women who had completed primary breast cancer treatments but had not started endocrine therapy found associations between subjective cognitive complaints and performance on

some neuropsychological tests, particularly for those who had received both chemotherapy and radiotherapy (30).

The profile emerging from the plethora of studies is one of a mild cognitive impairment affecting learning and memory, processing speed and executive function (31). The mechanisms underlying the phenomenon are not clear but suggestions include stress and coping styles (32), direct neurotoxic injury, telomere shortening, oxidative stress, cytokine dysregulation, estrogen-mediated effects, and genetic polymorphisms (33). Pro-inflammatory cytokines can be used as markers for cognitive function in neurological disease, and recent literature suggests that elevated levels of peripheral pro-inflammatory cytokines may be related to cognitive problems in cancer patients (34). Additionally, decreased estrogen levels may serve as a link between multiple mechanisms potentiating the effects, particularly in those women who experience an acute menopause following treatment.

Imaging studies have documented structural changes to the brain after completion of chemotherapy (35); again, however, some structural differences may have already been present before starting chemotherapy (36).

The literature to date shows that in order to get a true understanding of the extent of this phenomenon, a multi-faceted approach is required. Well-designed prospective studies are needed. These would ideally assess women prior to breast surgery, use matched control groups, incorporate imaging and biological measures and records of all the additional “side effects” of treatments that could contribute to poor cognitive functioning, for example, anxiety, pain, fatigue and sleep disturbance. Having a good pre-illness measure of how someone is functioning, the work they do, their family

commitments and ability to cope with changes in their life is also important in order to measure the real life impact on the patient.

Communication

Communication affects adjustment to the diagnosis and patient decision-making about treatment. The increasing complexity of our understanding about breast cancer and the number of therapeutic options now available has made discussions between patients and doctors very much more difficult. Breast cancer is no longer a simple disease to explain and patients already experiencing emotional turmoil enter a strange new world of esoteric language and concepts. Helping patients navigate their way through all this to ensure that they can genuinely provide educated and informed consent to treatment plans demands excellent communication skills from the healthcare professionals involved with breast cancer care. There are also some good web-based information sources available on YouTube, together with DVDs, leaflets and booklets describing treatment options, outcomes with and without treatment, uncertainties and clinical trial enrollment. A Cochrane review of 55 trials of 23 different screening/treatment decision support tools revealed that women who accessed them showed increased knowledge, more accurate risk perceptions, greater comfort with their decisions, and engaged in greater participation in decision-making (37).

An issue worthy of more research concerns the gross disparities that exist in survival outcomes among patients in groups with different socio-economic status (SES). Not only do those in lower SES groups have less time with healthcare professionals, but they are also not confident when asking for explanations about care plans and are

unlikely to access on-line informational sources or support services shown to help others in higher SES groupings.

Metastatic Breast Cancer

There has been far less psychosocial research in MBC compared to that in early disease. Women worldwide with advanced breast cancer attest to the sense of abandonment and neglect that they frequently feel (38). In a US study of expressive therapeutic writing in 176 women with MBC (39) 48% reported difficulty talking to others, often denying the severity of their illness or prognosis to close friends and relatives. Most had experienced shock, isolation, and a loss of control. As far as the need for further treatment was concerned, hair loss caused many 'devastation'. Most activities of daily living changed substantially. Their primary physical problems of fatigue and pain led to them cancel activities, which caused guilt. For some, the inability to work was a major challenge, and frequent medical appointments produced emotional strain. Almost all found the impact on their families distressing. Clearly much more work needs to be done to help women unfortunate enough to develop metastatic disease.

Conclusions

It is debatable as to whether or not the provision of psychosocial care has kept pace with advances in breast cancer treatment. There is however a growing consensus that psychosocial care should be well-integrated into routine cancer care with an emphasis on changing from how long to how well patients live (40). There are good suggestions as to how this might be achieved in the developed world where resources are more likely to be available, but even in these communities, ensuring access for different ethnic and minority groups needs more effort (40). Although

worldwide, the provision and receipt of psychosocial care remains patchy, three developments in the past decade do enhance the likelihood that it will eventually become a component of comprehensive cancer care: 1) we are much better able to define standards; 2) many organizations have developed and are updating useful clinical practice guidelines; and 3) there has also been some excellent work in the development and implementation of measurable quality indicators.

So are we getting better at enhancing survivorship in breast cancer? The answer is probably yes, but improvements have been mainly seen in early breast cancer not metastatic breast cancer, which needs addressing. Obviously, it remains important that there is global access to the best treatments and that thought is also given to the preferred routes of administration. We need to have systematic monitoring of side-effects of treatment to permit early implementation of evidence-based interventions that might include more integrative oncology utilizing, where appropriate, non-pharmacological modalities. There is still work to be done ensuring that all healthcare professionals have the communication skills required so they are capable of providing women with good, consistent, timely, accurate and understandable information.

Women's reactions to breast cancer and its treatment vary enormously irrespective of culture or class divides. For some, the diagnosis is a catastrophe, irreparably threatening their physical, functional, social, psychological, sexual and occupational well-being. For others it represents yet one more of life's hurdles to overcome together with other social, educational and financial iniquities they face.

Consequently, just as with the exciting advent of personalized and targeted medicine, we need similar endeavours producing more individualized psychosocial

care; communication should be flexible, adapted to the varying needs of individuals; appropriate screening should enable resources--counseling, relaxation therapy, yoga, exercise or mindfulness training--to be focused on those at most risk of the unremitting psychosocial dysfunction that compromises healthy survivorship.

Spreading scarce supportive services thinly for all irrespective of their need or risk of poor adjustment, makes as much sense as administering hormone treatment or trastuzumab without information about receptor status.

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